```
=> s levosimendan/cn
L1             1 LEVOSIMENDAN/CN

=> d l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS
RN   141505-33-1  REGISTRY
CN   Propanedinitrile, [[4-[(4R)-1,4,5,6-tetrahydro-4-methyl-6-oxo-3-
     pyridazinyl]phenyl]hydrazono]- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Propanedinitrile, [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-
     pyridazinyl)phenyl]hydrazono]-, (R)-
OTHER NAMES:
CN   (-)-OR 1259
CN   (R)-Simendan
CN   Levosimendan
CN   OR 1259
CN   Simdax
FS   STEREOSEARCH
MF   C14 H12 N6 O
SR   World Health Organization
LC   STN Files:   ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CAPLUS, CBNB, CIN, DDFU, DRUGNL, DRUGPAT, DRUGU,
       DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PHARMASEARCH, PROMT,
       SYNTHLINE, TOXCENTER, USAN, USPATFULL
         (*File contains numerically searchable property data)

Absolute stereochemistry.
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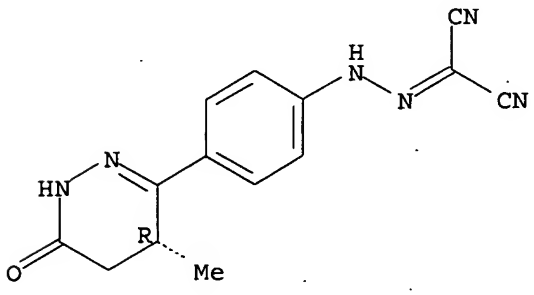


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

            111 REFERENCES IN FILE CA (1957 TO DATE)
              1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
            114 REFERENCES IN FILE CAPLUS (1957 TO DATE)


=>  FIL REGISTRY

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     8.70       9.54

FILE 'REGISTRY' ENTERED AT 11:20:51 ON 27 MAY 2003
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Property values tagged with IC are from the ZIC/VINITI data file
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STRUCTURE FILE UPDATES: 26 MAY 2003 HIGHEST RN 520505-31-1
DICTIONARY FILE UPDATES: 26 MAY 2003 HIGHEST RN 520505-31-1

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> SET TERMSET E#

SET COMMAND COMPLETED

=> DEL SEL Y

=> SEL L1 1 RN

E1 THROUGH E1 ASSIGNED

=> S E1/RN

L2 1 141505-33-1/RN

=> SET TERMSET LOGIN

SET COMMAND COMPLETED

=> FIL MRCK

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.48	10.02

FILE 'MRCK' ENTERED AT 11:20:56 ON 27 MAY 2003

FILE COVERS FROM LATE 19TH CENTURY TO PRESENT. LAST UPDATE: NOV 2002

=> S L2

L3 1 L2

=> DIS L3 1 SAM

L3 ANSWER 1 OF 1 MRCK
MERCK Number (MNO): 5491
CAS Registry No. (RN): **141505-33-1**
MERCK Index Name (MIN): Levosimendan
Molecular Form. (MF): C14 H12 N6 O

Available Display Fields (FA):

Code	Field Name
RN	CAS Registry Number
CN	Chemical Name
CN	Chemical Name (Drug Code)
CN	Chemical Name (CAS Index Name)
CN	Chemical Name (Synonym)
CN	Chemical Name (Trade Name)
COMP	Elemental Composition (by weight)
MP	Melting Point
MF	Molecular Formula
MW	Molecular Weight
ORP	Optical Rotatory Power
OCPP	Other Chemical and Physical Properties
RPN	Referenced Patent Number
THER	Therapeutic Category
TOX	Toxicity

=> fil caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.31	10.33

FILE 'CAPLUS' ENTERED AT 11:21:44 ON 27 MAY 2003
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FILE COVERS 1907 - 27 May 2003 VOL 138 ISS 22
FILE LAST UPDATED: 26 May 2003 (20030526/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l1
L4 113 L1

=> s l4 and pH
1147876 PH
L5 8 L4 AND PH

=> d l5 1-8

L5 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 2002:470297 CAPLUS
DN 138:242993
TI Development of level A, B and C in vitro-in vivo correlations for modified-release levosimendan capsules
AU Kortejarvi, H.; Mikkola, J.; Backman, M.; Antila, S.; Marvola, M.

CS Orion Pharma, Espoo, 02101, Finland
SO International Journal of Pharmaceutics (2002), 241(1), 87-95
CODEN: IJPHDE; ISSN: 0378-5173
PB Elsevier Science B.V.
DT Journal
LA English
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 2001:906809 CAPLUS
DN 137:72913
TI Effects of levosimendan, a novel inotropic calcium-sensitizing drug, in experimental septic shock
AU Oldner, Anders; Konrad, David; Weitzberg, Eddie; Rudehill, Anders; Rossi, Patrik; Wanecek, Michael
CS Department of Surgical Sciences, Section of Anaesthesiology and Intensive Care Medicine, Karolinska Institute, Stockholm, Swed.
SO Critical Care Medicine (2001), 29(11), 2185-2193
CODEN: CCMDC7; ISSN: 0090-3493
PB Lippincott Williams & Wilkins
DT Journal
LA English
RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 2000:719370 CAPLUS
DN 134:76296
TI Transdermal delivery of levosimendan
AU Valjakka-Koskela, R.; Hirvonen, J.; Monkkonen, J.; Kiesvaara, J.; Antila, S.; Lehtonen, L.; Urtti, A.
CS Pharmaceutical Development Department, Orion Corporation Orion Pharma, Kuopio, 70701, Finland
SO European Journal of Pharmaceutical Sciences (2000), 11(4), 343-350
CODEN: EPSCED; ISSN: 0928-0987
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 2000:622118 CAPLUS
DN 133:344385
TI Levosimendan improves diastolic and systolic function in failing human myocardium
AU Janssen, P. M. L.; Datz, N.; Zeitz, O.; Hasenfuss, G.
CS Abt. Kardiologie und Pneumologie, Universitat Gottingen, Gottingen, Germany
SO European Journal of Pharmacology (2000), 404(1/2), 191-199
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 2000:191448 CAPLUS
DN 133:26467
TI Further Evidence for the Cardiac Troponin C Mediated Calcium Sensitization by Levosimendan: Structure-response and Binding Analysis with Analogs of Levosimendan

AU Levijoki, Jouko; Pollesello, Piero; Kaivola, Juha; Tilgmann, Carola; Sorsa, Tia; Annila, Arto; Kilpelainen, Ilkka; Haikala, Heimo
CS Department of Drug Discovery & Pharmacology, Orion Pharma, Preclinical Research, Espoo, FIN-02101, Finland
SO Journal of Molecular and Cellular Cardiology (2000), 32(3), 479-491
CODEN: JMCDAY; ISSN: 0022-2828
PB Academic Press
DT Journal
LA English
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 1999:811225 CAPLUS
DN 132:40660
TI A reference compound for use in the analysis of levosimendan batches
IN Backstrom, Reijo; Heinonen, Tuula; Hauta-Aho, Tuula
PA Orion Corporation, Finland
SO PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9965888	A2	19991223	WO 1999-FI539	19990618
	WO 9965888	A3	20000127		
	W: AE, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	FI 9801428	A	19991219	FI 1998-1428	19980618
	CA 2334864	AA	19991223	CA 1999-2334864	19990618
	AU 9947863	A1	20000105	AU 1999-47863	19990618
	AU 755699	B2	20021219		
	BR 9911230	A	20010306	BR 1999-11230	19990618
	EP 1087956	A2	20010404	EP 1999-931312	19990618
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	NZ 508557	A	20020531	NZ 1999-508557	19990618
	JP 2002518383	T2	20020625	JP 2000-554714	19990618
	NO 2000006444	A	20001215	NO 2000-6444	20001215
	US 6340764	B1	20020122	US 2001-719806	20010220
PRAI	FI 1998-1428	A	19980618		
	WO 1999-FI539	W	19990618		

L5 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 1997:10659 CAPLUS
DN 126:112688
TI Enantiomeric bioanalysis of simendan and levosimendan by chiral high-performance liquid chromatography
AU Wikberg, Tom; Korkolainen, Tapio; Karlsson, Marianne
CS Orion-Farmos, Orion Res., Espoo, FIN-02101, Finland
SO Chirality (1996), 8(7), 511-517
CODEN: CHRLEP; ISSN: 0899-0042
PB Wiley-Liss
DT Journal
LA English

L5 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 1995:521629 CAPLUS
DN 122:255986
TI Troponin C-mediated calcium sensitization induced by levosimendan does not

impair relaxation
AU Haikala, Heimo; Nissinen, Erkki; ERtemadzadeh, Ehsan; Levijoki, Jouko; Linden, Inge-Britt
CS Orion-Farmos, Orion Research, Espoo, Finland
SO Journal of Cardiovascular Pharmacology (1995), 25(5), 794-801
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott-Raven
DT Journal
LA English

=> d l5 1-8 full
'FULL' IS NOT A VALID FORMAT FOR FILE 'CAPLUS'

The following are valid formats:

ABS --------- GI and AB
ALL --------- BIB, AB, IND, RE
APPS -------- AI, PRAI
BIB --------- AN, plus Bibliographic Data and PI table (default)
CAN --------- List of CA abstract numbers without answer numbers
CBIB -------- AN, plus Compressed Bibliographic Data
DALL -------- ALL, delimited (end of each field identified)
DMAX -------- MAX, delimited for post-processing
FAM --------- AN, PI and PRAI in table, plus Patent Family data
FBIB -------- AN, BIB, plus Patent FAM
IND --------- Indexing data
IPC --------- International Patent Classifications
MAX --------- ALL, plus Patent FAM, RE
PATS -------- PI, SO
SAM --------- CC, SX, TI, ST, IT
SCAN -------- CC, SX, TI, ST, IT (random display, no answer numbers; SCAN must be entered on the same line as the DISPLAY, e.g., D SCAN or DISPLAY SCAN)
STD --------- BIB, IPC, and NCL

IABS -------- ABS, indented with text labels
IALL -------- ALL, indented with text labels
IBIB -------- BIB, indented with text labels
IMAX -------- MAX, indented with text labels
ISTD -------- STD, indented with text labels

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

HIT --------- Fields containing hit terms
HITIND ------ IC, ICA, ICI, NCL, CC and index field (ST and IT) containing hit terms
HITRN ------- HIT RN and its text modification
HITSTR ------ HIT RN, its text modification, its CA index name, and its structure diagram
HITSEQ ------ HIT RN, its text modification, its CA index name, its structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its structure diagram, plus NTE and SEQ fields
KWIC -------- Hit term plus 20 words on either side
OCC --------- Number of occurrence of hit term and field in which it occurs

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codes. For a list of the display field codes, enter HELP DFIELDS at an arrow prompt (=>). Examples of formats include: TI; TI,AU; BIB,ST; TI,IND; TI,SO. You may specify the format fields in any order and the information will be displayed in the same order as the format specification.

All of the formats (except for SAM, SCAN, HIT, HITIND, HITRN, HITSTR, FHITSTR, HITSEQ, FHITSEQ, KWIC, and OCC) may be used with DISPLAY ACC to view a specified Accession Number.
ENTER DISPLAY FORMAT (BIB):all

L5 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 2002:470297 CAPLUS
DN 138:242993
TI Development of level A, B and C in vitro-in vivo correlations for modified-release levosimendan capsules
AU Kortejarvi, H.; Mikkola, J.; Backman, M.; Antila, S.; Marvola, M.
CS Orion Pharma, Espoo, 02101, Finland
SO International Journal of Pharmaceutics (2002), 241(1), 87-95
CODEN: IJPHDE; ISSN: 0378-5173
PB Elsevier Science B.V.
DT Journal
LA English
CC 63-5 (Pharmaceuticals)
AB The aim of this study was to investigate the possibility of developing different levels of correlation between in vitro release and in vivo absorption rate for four modified-release levosimendan capsule formulations. Differences and similarities in the in vitro dissoln. curves were compared with pharmacokinetic parameters describing absorption rate. Formulations F, G, H and I differed in the amts. of the delaying excipients alginic acid and hydroxypropyl Me cellulose. In vitro release rate was studied by the USP basket method using the following conditions: **pH** 5.8 or 7.4 and a rotation speed of 50 or 100 rpm. In vivo bioavailability was tested in nine healthy male volunteers and the fractions absorbed were calcd. by the Wagner-Nelson method. Dissoln. conditions **pH** 5.8 and a rotation speed of 100 rpm predicted best the similarities and differences in absorption rates among different formulations, and levels C and B correlation coeffs. were 0.85 and 0.97, resp. For formulation H level A correlation (r = 0.997) was found when in vitro lag time was 0.2 h and time scale factor 1.9. This study indicated that dissoln. tests developed can be used as a surrogate for human bioequivalence studies, for development processes of final com. products, to ensure batch to batch bioequivalence and in the future in possible scale-up and post approval change cases for modified-release levosimendan formulation H.
ST bioavailability levosimendan capsule
IT Drug delivery systems
(capsules, modified-release; development of level A, B and C in vitro-in vivo correlations for modified-release levosimendan capsules)
IT Dissolution
Drug bioavailability
Human
(development of level A, B and C in vitro-in vivo correlations for modified-release levosimendan capsules)
IT 57-11-4, Stearic acid, biological studies 9004-65-3, Hydroxypropyl methyl cellulose 9005-32-7, Alginic acid
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(development of level A, B and C in vitro-in vivo correlations for modified-release levosimendan capsules)
IT **141505-33-1**, Levosimendan
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(development of level A, B and C in vitro-in vivo correlations for

modified-release levosimendan capsules)
IT 9004-34-6, Cellulose, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(microcryst.; development of level A, B and C in vitro-in vivo correlations for modified-release levosimendan capsules)
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Amidon, G; Pharm Res 1995, V3, P413
(2) Antila, S; Eur J Pharm Sci 1999, V9, P85 CAPLUS
(3) Brockmeier, D; Areneim Forsch/Drug Res 1983, V33, P598 MEDLINE
(4) Cardot, J; Eur J Metab Pharmacokinet 1993, V1, P113
(5) Cutler, D; Int J Pharm 1997, V158, P185 CAPLUS
(6) Hernandez, R; Int J Pharm 1996, V139, P45 CAPLUS
(7) Karlsson, M; Biomed Chromatogr 1997, V11, P54 CAPLUS
(8) Leeson, L; Drug Inf J 1995, V29, P903
(9) Lilleberg, J; J Cardiovasc Pharmacol 1995, V26(Suppl 1), P63
(10) Moore, J; Pharm Tech 1996, V20(6), P64
(11) Munday, D; Int J Pharm 1995, V118, P251 CAPLUS
(12) Sandell, E; J Cardiovasc Pharmacol 1995, V26, PS57 CAPLUS
(13) Skelly, J; Pharm Res 1990, V9, P975
(14) Sunberg, S; Int J Clin Pharmacol Ther 1998, V36, P629
(15) Takahashi, R; Eur J Pharmacol 2000, V400, P103 CAPLUS
(16) Wagner, J; J Pharm Sci 1964, V53, P1392 CAPLUS
(17) Yu, Z; Biopharm Drug Dispos 1996, V17, P259 CAPLUS

L5 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 2001:906809 CAPLUS
DN 137:72913
TI Effects of levosimendan, a novel inotropic calcium-sensitizing drug, in experimental septic shock
AU Oldner, Anders; Konrad, David; Weitzberg, Eddie; Rudehill, Anders; Rossi, Patrik; Wanecek, Michael
CS Department of Surgical Sciences, Section of Anaesthesiology and Intensive Care Medicine, Karolinska Institute, Stockholm, Swed.
SO Critical Care Medicine (2001), 29(11), 2185-2193
CODEN: CCMDC7; ISSN: 0090-3493
PB Lippincott Williams & Wilkins
DT Journal
LA English
CC 1-8 (Pharmacology)
AB Levosimendan is a novel inodilator that improves cardiac contractility by sensitizing troponin C to calcium. This drug has proved to be effective in treating advanced congestive heart failure but has not been evaluated in septic settings. The purpose of the present study was to study the effects of this drug in a porcine model of endotoxemia in a prospective exptl. study. All animals (fourteen land-race pigs) were anesthetized and catheterized for measurement of central and pulmonary hemodynamics. Ultrasonic flow probes were placed around the renal artery and portal vein to measure blood flow. A tonometer was placed in the ileum to measure mucosal **pH**. Levosimendan was given to six animals as a bolus (200 .mu.g.cntdot.kg-1) followed by a continuous infusion (200 .mu.g.cntdot.kg-1-hr-1). Thirty minutes after onset of levosimendan treatment, all animals received endotoxin (20 .mu.g.cntdot.kg-1-hr-1 for 3 h). At baseline, levosimendan induced a systemic vasodilation with a redn. in blood pressure and an increase in heart rate. A tendency to an increase in cardiac index did not reach statistical significance (p = .055). Cardiac index and systemic oxygen delivery were markedly improved in the levosimendan group during endotoxemia. Systemic vascular resistance and blood pressure were reduced in the levosimendan group. The latter parameter, however, was only different from the control group during the initial phase of endotoxin shock but not at the late, most pronounced phase of shock. Levosimendan also efficiently attenuated endotoxin-induced pulmonary hypertension. Portal venous blood flow and

gut oxygen delivery were improved, but no concomitant redn. in endotoxin-induced intestinal mucosal acidosis was obsd. Renal blood flow was unaffected, as was the endotoxin-induced increase in plasma endothelin-1-like immunoreactivity. These findings support previous reports of calcium desensitization as a potential component in septic myocardial depression. Furthermore, the vasodilatory properties of this drug were well tolerated in the current model of hypodynamic endotoxin shock, and they may have contributed to improved regional blood flow as seen in the gut as well as improved systemic perfusion by means of reduced biventricular afterload. Pretreatment with levosimendan in pigs subjected to endotoxin shock improved cardiac output and systemic and gut oxygen delivery. In addn., pulmonary hypertension largely was attenuated without any adverse effects on gas exchange. These results are promising in several aspects, but the role of levosimendan in the treating circulatory failure in sepsis remains to be established.

ST inotropic calcium sensitizer levosimendan septic shock heart failure

IT Heart, disease
(failure; inotropic calcium-sensitizing drug levosimendan effect in septic shock)

IT Cardiovascular system
Circulation
Endotoxemia
Inotropics
Vasodilators
(inotropic calcium-sensitizing drug levosimendan effect in septic shock)

IT Heart, disease
(myocarditis, septic; inotropic calcium-sensitizing drug levosimendan effect in septic shock)

IT Antihypertensives
Hypertension
(pulmonary; inotropic calcium-sensitizing drug levosimendan effect in septic shock)

IT Shock (circulatory collapse)
(septic; inotropic calcium-sensitizing drug levosimendan effect in septic shock)

IT 7440-70-2, Calcium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inotropic calcium-sensitizing drug levosimendan effect in septic shock)

IT **141505-33-1**, Levosimendan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inotropic calcium-sensitizing drug levosimendan effect in septic shock)

RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Angus, D; Crit Care Med 2000, V28, PA48
(2) Archer, S; Adv Exp Med Biol 2000, V475, P219 CAPLUS
(3) Bernard, G; N Engl J Med 2001, V344, P699 CAPLUS
(4) Biffl, W; Br J Anaesth 1996, V77, P59 MEDLINE
(5) Carrico, C; Arch Surg 1986, V121, P196 MEDLINE
(6) Czaika, G; Muscle Nerve 2000, V23, P967 CAPLUS
(7) Doglio, G; Crit Care Med 1991, V19, P1037 MEDLINE
(8) Edes, I; Circ Res 1995, V77, P107 CAPLUS
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(10) Gutierrez, G; Lancet 1992, V339, P195 MEDLINE
(11) Harjola, V; Am J Cardiol 1999, V83, P4 CAPLUS
(12) Harkin, C; J Cardiovasc Pharmacol 1995, V26, P179 CAPLUS
(13) Hayes, J; Acta Anaesthesiol Sin 1998, V36, P113 MEDLINE
(14) Hemsen, A; Acta Physiol Scand 1991, V602(Suppl), P1
(15) Hollenberg, S; J Heart Lung Transplant 1997, V16, PS7 MEDLINE
(16) Hung, J; Circ Res 1993, V73, P125 CAPLUS
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(18) Jakob, S; Br J Anaesth 1999, V83, P740 MEDLINE
(19) Landry, D; J Clin Invest 1992, V89, P2071 CAPLUS
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(22) Ming, M; Shock 2000, V13, P459 MEDLINE
(23) Nicklas, J; Am J Cardiol 1999, V83, P12 CAPLUS
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(25) Oldner, A; Gut 1998, V42, P696 CAPLUS
(26) Oldner, A; Splanchnic Organ Homeostasis in Experimental Endotoxin Shock: With Special Reference to the Endothelin and Renin-Angiotensin Systems 1999
(27) Pagel, P; Br J Pharmacol 1996, V119, P609 CAPLUS
(28) Rubanyi, G; Pharmacol Rev 1994, V46, P325 CAPLUS
(29) Silverman, H; Crit Care Med 1993, V21, P31 MEDLINE
(30) Suffredini, A; Schweiz Med Wochenschr 1998, V128, P1444 MEDLINE
(31) Udvary, E; Br J Pharmacol 1995, V114, P656 CAPLUS
(32) Vanelli, G; Exp Physiol 1995, V80, P167 CAPLUS
(33) Wanecek, M; Eur J Pharmacol 2000, V407, P1 CAPLUS
(34) Wanecek, M; Shock 1997, V7, P364 MEDLINE
(35) Yasuda, S; Circ Res 1997, V81, P1011 CAPLUS
(36) Yokoshiki, H; J Pharmacol Exp Ther 1997, V283, P375 CAPLUS

L5 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 2000:719370 CAPLUS
DN 134:76296
TI Transdermal delivery of levosimendan
AU Valjakka-Koskela, R.; Hirvonen, J.; Monkkonen, J.; Kiesvaara, J.; Antila, S.; Lehtonen, L.; Urtti, A.
CS Pharmaceutical Development Department, Orion Corporation Orion Pharma, Kuopio, 70701, Finland
SO European Journal of Pharmaceutical Sciences (2000), 11(4), 343-350
CODEN: EPSCED; ISSN: 0928-0987
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
AB The aim of this study was to det. if transdermal penetration of levosimendan, a novel pos. inotropic drug, was enhanced and controlled by formulation modifications. Penetration of levosimendan across human epidermis in vitro was detd. using abdominal excised skin and diffusion cells. Predicted steady-state plasma concns. of levosimendan were estd. using permeabilities and pharmacokinetic parameters of levosimendan. For penetration enhancement we used different **pH** values, co-solvents, cyclodextrins, surfactants, penetration enhancers, liposomes, and iontophoresis. Sodium lauryl sulfate, ethanol, oleic acid, and soya phosphatidylcholine or their combinations clearly increased levosimendan permeation across the skin in vitro. Iontophoresis was also an efficient method to increase transdermal permeation of levosimendan. A hydrophilic co-solvent/penetration enhancer is needed to achieve better permeability of levosimendan across the skin. Thus, transdermal delivery of levosimendan can be significantly increased by formulation modification. Based on kinetic calcns., therapeutic plasma concns. may be achievable transdermally.
ST transdermal delivery levosimendan
IT Skin
(epidermis; transdermal delivery of levosimendan)
IT Biological transport
(permeation; transdermal delivery of levosimendan)
IT Phosphatidylcholines, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(soya; transdermal delivery of levosimendan)
IT Critical micelle concentration
Drug bioavailability
Iontophoresis

Permeation enhancers
Skin
Solubilization
(transdermal delivery of levosimendan)

IT **141505-33-1**, Levosimendan
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(transdermal delivery of levosimendan)

IT 64-17-5, Ethanol, biological studies 112-80-1, Oleic acid, biological studies 151-21-3, Sodium lauryl sulfate, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(transdermal delivery of levosimendan)

RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L5 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2003 ACS

AN 2000:622118 CAPLUS
DN 133:344385

TI Levosimendan improves diastolic and systolic function in failing human myocardium

AU Janssen, P. M. L.; Datz, N.; Zeitz, O.; Hasenfuss, G.
CS Abt. Kardiologie und Pneumologie, Universitat Gottingen, Gottingen, Germany

SO European Journal of Pharmacology (2000), 404(1/2), 191-199
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
CC 1-8 (Pharmacology)

AB Ca2+-sensitizers increase myocardial contractility, but may worsen diastolic dysfunction. Levosimendan, through its unique troponin-C interaction, may preserve diastolic function. We investigated the effects of levosimendan (10-7-10-5 M) on diastolic and systolic function in multicellular cardiac muscle prepns. from end-stage failing human hearts (1 and 2.5 Hz, 37.degree.C, 1.25 mM [Ca2+], **pH** 7.4). Levosimendan improved systolic function: at 1 Hz, developed force (Fdev) increased from 13.84.+-.3.27 to 16.40.+-.3.57 (10-7 M, P<0.05), while

diastolic force (Fdia) decreased from 5.32.+-.0.67 to 4.94.+-.0.61 mN/mm2 (P<0.05). Under control conditions, the increase in stimulation frequency from 1 to 2.5 Hz resulted in a decrease in Fdev of -0.51.+-.1.80 mN/mm2 (neg. force-frequency relationship). Levosimendan improved this relationship: at 10-7 M, this change became pos. (+1.81.+-.2.06 mN/mm2, P<0.05). Diastolic function was markedly improved in the presence of levosimendan; the increase in Fdia of 1.56.+-.0.42 mN/mm2 (control) was attenuated to 0.70.+-.0.19 mN/mm2 (P<0.05). To allow for a more detailed anal., prepns. were sometimes divided into two groups, based on their force-frequency behavior. Twitch timing parameters were accelerated by levosimendan in prepns. with a neg. force-frequency relationship. Levosimendan improves both systolic and diastolic function in failing human myocardium. Effects are even more pronounced at higher heart rates and under prevailing diastolic dysfunction.

ST levosimendan diastolic systolic function heart failure

IT Blood pressure
(diastolic; levosimendan improves diastolic and systolic function in failing human myocardium)

IT Heart, disease
(failure; levosimendan improves diastolic and systolic function in failing human myocardium)

IT Cardiac contraction
Inotropics
(levosimendan improves diastolic and systolic function in failing human myocardium)

IT Blood pressure
(systolic; levosimendan improves diastolic and systolic function in failing human myocardium)

IT **141505-33-1**, Levosimendan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(levosimendan improves diastolic and systolic function in failing human myocardium)

IT 7440-70-2, Calcium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sensitizers; levosimendan improves diastolic and systolic function in failing human myocardium)

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L5 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 2000:191448 CAPLUS
DN 133:26467
TI Further Evidence for the Cardiac Troponin C Mediated Calcium Sensitization by Levosimendan: Structure-response and Binding Analysis with Analogs of Levosimendan
AU Levijoki, Jouko; Pollesello, Piero; Kaivola, Juha; Tilgmann, Carola; Sorsa, Tia; Annila, Arto; Kilpelainen, Ilkka; Haikala, Heimo
CS Department of Drug Discovery & Pharmacology, Orion Pharma, Preclinical Research, Espoo, FIN-02101, Finland
SO Journal of Molecular and Cellular Cardiology (2000), 32(3), 479-491
CODEN: JMCDAY; ISSN: 0022-2828
PB Academic Press
DT Journal
LA English
CC 1-3 (Pharmacology)
AB Levosimendan, an inodilatory drug discovered using troponin C as a target protein, has a cardiac effect deriving from the calcium sensitization of contractile proteins. The aim of this study was to give further evidence that levosimendan binds to cardiac troponin C and that the binding involves amino acid residues on helix.epsilon. of the N-terminal domain of this calcium-binding protein. Nine org. mols., obtained by chem. modification of levosimendan, were tested both for their calcium-dependent binding to troponin C and troponin complex affinity HPLC columns, and for their ability to increase the calcium sensitivity of myofilaments in cardiac skinned fibers. A good correlation between the calcium sensitization and the calcium-dependent binding to troponin complex (r=0.90) and to cardiac troponin C (r=0.91) for the analogs of levosimendan was shown. In addn., the effect of levosimendan on the calcium-induced conformational changes in native and point-mutated cTnC was studied. Cys84 Ser, Asp87 Lys and Asp88 Ala point-mutated cTnC were shown to maintain a high affinity to calcium, but their Ca2+titrn. curves were not influenced by levosimendan as for the native protein. Finally, it was demonstrated that the NMR chem. shifts of the terminal Me groups of Met47, Met81, and Met85 on calcium-satd. cTnC were changed after addn. of levosimendan in water soln. at **pH** 7.4. This effect was not seen when adding an analog of levosimendan, which did not bind to the troponin C affinity HPLC column and did not increase the calcium-induced tension in cardiac skinned fibers. (c) 2000 Academic Press.
ST levosimendan analog heart troponin calcium sensitization; structure activity levosimendan inotropic calcium troponin
IT Troponins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(C; cardiac troponin C mediated calcium sensitization by levosimendan, structure-response and binding anal. with analogs of levosimendan)
IT Inotropics
Structure-activity relationship
(cardiac troponin C mediated calcium sensitization by levosimendan, structure-response and binding anal. with analogs of levosimendan)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(contractile; cardiac troponin C mediated calcium sensitization by levosimendan, structure-response and binding anal. with analogs of

levosimendan)
IT 306-18-3 131741-03-2 131741-04-3 131741-19-0 131741-25-8
131741-42-9 **141505-33-1**, Levosimendan 274263-64-8
274263-65-9
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cardiac troponin C mediated calcium sensitization by levosimendan, structure-response and binding anal. with analogs of levosimendan)
IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(sensitization; cardiac troponin C mediated calcium sensitization by levosimendan, structure-response and binding anal. with analogs of levosimendan)
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
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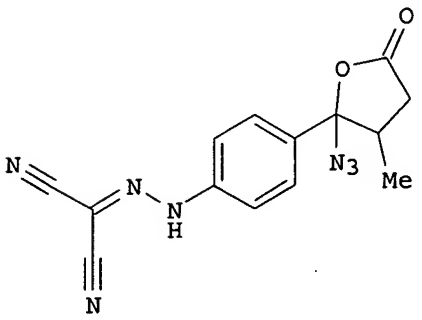
L5 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 1999:811225 CAPLUS
DN 132:40660
TI A reference compound for use in the analysis of levosimendan batches
IN Backstrom, Reijo; Heinonen, Tuula; Hauta-Aho, Tuula
PA Orion Corporation, Finland
SO PCT Int. Appl., 13 pp.

CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D307-00
CC 64-3 (Pharmaceutical Analysis)
Section cross-reference(s): 28
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9965888	A2	19991223	WO 1999-FI539	19990618
	WO 9965888	A3	20000127		
	W: AE, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	FI 9801428	A	19991219	FI 1998-1428	19980618
	CA 2334864	AA	19991223	CA 1999-2334864	19990618
	AU 9947863	A1	20000105	AU 1999-47863	19990618
	AU 755699	B2	20021219		
	BR 9911230	A	20010306	BR 1999-11230	19990618
	EP 1087956	A2	20010404	EP 1999-931312	19990618
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	NZ 508557	A	20020531	NZ 1999-508557	19990618
	JP 2002518383	T2	20020625	JP 2000-554714	19990618
	NO 2000006444	A	20001215	NO 2000-6444	20001215
	US 6340764	B1	20020122	US 2001-719806	20010220
PRAI	FI 1998-1428	A	19980618		
	WO 1999-FI539	W	19990618		

GI



I

AB I is used as a ref. compd. in the detn. of potentially genotoxic impurities in levosimendan samples. The invention also relates to an analytic method for the detn. of potentially genotoxic impurities in levosimendan samples wherein I is used as a ref. compd. Levosimendan is a medicament useful in the treatment of heart failure. To a a soln. of 153 g 6-(4-aminophenyl)4,5-dihydro-5-methyl-3(2H)-pyridazinone in 750 mL acetic acid was slowly added 210 g of sodium nitrite at 10-20.degree.. The reaction mixt. was poured rapidly to 20.degree. soln. of 150g malononitrile in 1500 mL water and stirred at 20-25.degree. for 60 min, then filtered and washed with water. The wet solid was extd. successively with THF and Et acetate, then dried and the solvent evapd. The residue was purified to obtain[[4-(2-azido-3-methyl-5-oxotetrahydro-furan-2-yl)phenyl]hydrazono]propanedinitrile (II) (a mixt. of diastereomers). II was used as ref. compd. in HPLC of levosimendan with UV detection at 360 nm and the mobile phase of acetonitrile and phosphate buffer **pH** = 2.1.

ST pyridazinyl deriv ref levosimendan analysis

IT HPLC
Mutagens
(ref. compd. for use in anal. of levosimendan batches)
IT 252638-01-0P
RL: ANT (Analyte); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation)
(ref. compd. for use in anal. of levosimendan batches)
IT **141505-33-1**, Levosimendan
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(ref. compd. for use in anal. of levosimendan batches)
IT 109-77-3, Malononitrile 7632-00-0, Sodium nitrite
RL: RCT (Reactant); RACT (Reactant or reagent)
(ref. compd. for use in anal. of levosimendan batches)

L5 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 1997:10659 CAPLUS
DN 126:112688
TI Enantiomeric bioanalysis of simendan and levosimendan by chiral high-performance liquid chromatography
AU Wikberg, Tom; Korkolainen, Tapio; Karlsson, Marianne
CS Orion-Farmos, Orion Res., Espoo, FIN-02101, Finland
SO Chirality (1996), 8(7), 511-517
CODEN: CHRLEP; ISSN: 0899-0042
PB Wiley-Liss
DT Journal
LA English
CC 1-1 (Pharmacology)
AB Rac-Simendan, (.+-.)-(R,S)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile, and the levorotatory enantiomer levosimendan, are drug candidates intended for the treatment of congestive heart failure. An enantiospecific high-performance liq. chromatog. (HPLC) method suitable for detn. of the ratio of the enantiomer concns. in blood plasma samples was developed. Direct resoln. of the enantiomers was achieved by using a chiral .beta.-cyclodextrin stationary phase in reversed phase mode. With an eluent contg. 24-33% of methanol in a 0.5% (vol./vol.) triethylammonium acetate buffer, **pH** 6.0, and a flow rate of 1 mL/min, a resoln. (1.2-1.6) adequate for the detns. was achieved. By using UV detection, the relative concn. of the enantiomers in plasma was assessed down to 10 ng/mL. For the racemate, the results indicated a slightly enantioselective disposition and plasma protein binding in rat, dog, and man. The pure enantiomer, levosimendan, was found not to isomerize in vivo.
ST simendan enantiomer detn blood HPLC
IT Blood analysis
HPLC
(enantiomeric bioanal. of simendan and levosimendan by chiral high-performance liq. chromatog.)
IT 131741-08-7, Simendan **141505-33-1**, Levosimendan 144238-75-5, Dextrosimendan
RL: ANT (Analyte); ANST (Analytical study)
(enantiomeric bioanal. of simendan and levosimendan by chiral high-performance liq. chromatog.)

L5 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 1995:521629 CAPLUS
DN 122:255986
TI Troponin C-mediated calcium sensitization induced by levosimendan does not impair relaxation
AU Haikala, Heimo; Nissinen, Erkki; ERtemadzadeh, Ehsan; Levijoki, Jouko; Linden, Inge-Britt
CS Orion-Farmos, Orion Research, Espoo, Finland
SO Journal of Cardiovascular Pharmacology (1995), 25(5), 794-801
CODEN: JCPCDT; ISSN: 0160-2446

PB Lippincott-Raven
DT Journal
LA English
CC 1-8 (Pharmacology)
AB Levosimendan is a novel pos. inotropic drug targeted to increase contraction force of the heart through its calcium-dependent binding to troponin C (cTnC). We investigated the calcium-sensitizing effect of levosimendan on contractile proteins as well as its pos. inotropic and lusitropic effects in paced guinea pig papillary muscle. We also studied the effect on energy consumption of myosin-actin crossbridges in a myosin ATPase assay. The calcium sensitization induced by levosimendan in fibers skinned with saponin was dependent on the perforation velocity of cell membranes. Levosimendan was almost ineffective in slowly perforated fibers, but it was the most potent calcium sensitizer in fibers with rapidly perforated cells. The perforation-dependent calcium sensitization was probably due to changes in phosphorylation state of contractile proteins during the slow dissection of fibers. It is noteworthy that the calcium-sensitizing effect of levosimendan was not affected by acidic **pH**. Levosimendan at the therapeutically relevant (0.3-10 .mu.M) concns. markedly increased calcium sensitivity both at **pH** 6.7 and 7.0, being more potent than EMD 53998, pimobendan, and MCI-154. The lack of effect of levosimendan on max. tension supports the hypothesis that levosimendan increases calcium sensitivity through its action on cTnC. Unlike EMD 53998, levosimendan did not increase myosin ATPase activity, indicating that it did not increase the cycling rate of myosin-actin crossbridges. In paced papillary muscles, levosimendan induced pos. inotropic effect without changing relaxation time. Thus, levosimendan was devoid of the main neg. factors described for calcium sensitizers.
ST inotropic levosimendan calcium sensitization heart relaxation; troponin C levosimendan calcium sensitization heart
IT Troponins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(troponin C-mediated calcium sensitization induced by ionotropic drug levosimendan does not impair relaxation of heart muscles)
IT Cardiotonics
(inotropics, troponin C-mediated calcium sensitization induced by ionotropic drug levosimendan does not impair relaxation of heart muscles)
IT 74150-27-9, Pimobendan 98326-33-1, MCI-154 120223-04-3, EMD 53998
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(calcium sensitization by inotropics and heart muscle relaxation)
IT **141505-33-1**, Levosimendan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(troponin C-mediated calcium sensitization induced by ionotropic drug levosimendan does not impair relaxation of heart muscles)
IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(troponin C-mediated calcium sensitization induced by ionotropic drug levosimendan does not impair relaxation of heart muscles)

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	42.38	52.71

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION

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REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2003
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2003

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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l1
L6 10 L1

=> s l6 and pH
339138 PH
L7 8 L6 AND PH

=> d l7 1-8 hit

L7 ANSWER 1 OF 8 USPATFULL
DETD The apparatus comprised a Gilson ASTED (Automated Sequential Trace Enrichment System) system (Gilson Medical Electronics, Villiers-le-Bel, France). The dialysis cell was fitted with a Cuprophan cellulose membrane with a molecular cut-off of 15 kDa and the trace enrichment column was a Hypersil ODS (5.8.times.4.6 mm i.d., 10 .mu.m). The chromatographic system consisted of an LKB Model 2150 pump (Bromma, Sweden) and a Lichrosorb RP-18 (250.times.4 mm i.d., 10 .mu.m) column (Merck, Darmstadt, Germany). The detector was a Spectra 100 UV-VIS (Spectra-Physics, San Jose, Calif., USA). The wavelength was 380 nm. The mobile phase consisted of a 32 mM monosodium dihydrogen phosphate buffer, methanol, and tetrahydrofuran (45:65:1, v/v/v, **pH** 3.5). The mobile phase flow rate was 1.0 ml/min.
DETD The release of levosimendan from the preparations was studied using the paddle method according to USP XXII. The dissolution medium was phosphate buffer **pH** 5.8. The rotation speed of the paddles 50 rpm.
IT **141505-33-1**, Levosimendan

(transmucosal formulations of levosimendan)

L7 ANSWER 2 OF 8 USPATFULL

DETD 100 g of racemic 6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone was added to 2997 ml of ethyl acetate, 94.4 ml of water, 77.8 g of D-tartaric acid and 1.0 g of D-tartaric salt of (-)-6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone under nitrogen. The mixture was stirred in 25.degree. C. for 1.5 h. The mixture was then heated to 65.degree. C. and stirred for 2 h. The precipitate was filtered hot and washed with 561 ml of ethyl acetate. The precipitate was mixed with 400 ml of water and **pH** of the mixture was adjusted to 9-10 with NH.sub.3. The mixture was cooled to 0.degree. C. and stirred for 2 h. The precipitate was filtered, washed three times with 322 ml of cold water and dried in vacuum in 50.degree. C. Yield was 35 g and the ratio of (-/+) enantiomers 93/7%. The product (35 g) was further added to 777 ml of acetonitrile and 2.0 g of celite under nitrogen. The precipitate was filtered hot and washed with 33 ml of acetonitrile which was added to the filtrate. 253 ml of acetonitrile was distilled from the filtrate and the remaining mixture was cooled to -5.degree. C. The precipitate was filtered, washed with 76 ml of acetonitrile and dried in vacuum in 50.degree. C. Yield 24.5 g. Ratio of (-/+) enantiomers 96/4%.

DETD The enantiomeric purities of the products were determined by the high performance liquid chromatography (HPLC). The enantiomers of compound (II) were separated by using a cellulose-type chiral column (Chiralcel OJ 25.times.0.46 cm). The mobile phase consisted of ethanol. The flow rate was 0.5 ml/min. The enantiomers of compound (I) were separated by using a .beta.-cyclodextrin column (Cyclobond I Beta, 4.6.times.250 mm). The mobile phase consisted of 36% methanol in water buffered to **pH** 6.0 with 1% triethylammonium acetate. The flow rate was 0.8 ml/min.

IT **141505-33-1P**, Levosimendan
(oral compns. contg. cryst. levosimendan for treatment of congestive heart disease)

L7 ANSWER 3 OF 8 USPATFULL

DETD The product of a levosimendan batch is preferably analyzed using High Pressure Liquid Chromatography (HPLC). Suitable apparatus include e.g. C-8 reversed phase HPLC column with UV-detection at 360 nm. The mobile phase is e.g. a mixture of phosphate buffer **pH** 2.1 and acetonitrile. The levosimendan sample is dissolved in suitable solvent such as a mixture of dimethyl sulfoxide, methanol and water. The reference solutions are prepared by dissolving compound (I) in suitable solvent. The retention times of levosimendan and compound (I) or diastereomers thereof are determined in the chromatographic conditions used. The amount of (I) in the levosimendan sample is determined by comparing the chromatograms obtained for the sample solution and the reference solution. The procedure is described in detail in Example 2.

DETD The HPLC (High Pressure Liquid Chromatography) method for analysis of compound (I) in levosimendan raw material was based on the C-8 reversed phase HPLC column with UV-detection at 360 nm. The mobile phase consisted of acetonitrile and phosphate buffer **pH** 2.1.

DETD 4. Phosphate buffer **pH** 2.1:

DETD Dissolve 1.8 g of sodium dihydrogen phosphate (NaH.sub.2PO.sub.4) in water and add 2.0 ml of phosphoric acid. Adjust the **pH** if necessary with 2 M sodium hydroxide or 1 M phosphoric acid. Dilute to 1000.0 ml with water.

DETD

Apparatus Liquid chromatograph
Detector UV-VIS, detection wavelength 360 nm
Column Symmetry C 8, 3.0 .mu.m, 7.5 cm .times. 4.6 mm
Oven temperature ambient
Mobile phase A: phosphate buffer **pH** 2.1

B: acetonitrile
% B 0 min 20%
5 min 30%
15 min 30%
30 min 90%
Flow rate 0.8 ml/min
Injection volume 100 .mu.l
Run time 30 min
Post time 10 min
Retention times: levosimendan about 13 min
Compound (I) minor diastereomer: about 24 min
Compound (I) major diastereomer: about 25 min
IT **141505-33-1**, Levosimendan
(ref. compd. for use in anal. of levosimendan batches)

L7 ANSWER 4 OF 8 USPATFULL
SUMM The preparation according to the invention may also include an antimicrobial agent, a preservative, an antioxidant and a **pH** -controlling agent and other additives known in the art.

DETD Transdermal penetration of levosimendan across human skin in vitro was studied with side-by-side diffusion chambers (DC-100, Crown Glass Co., Somerville, N.J.) at 25.degree. C. The receiver phase (3 ml) consisted of blank sodium phosphate buffer (**pH** 5.0). Each studied saturated levosimendan solution (3 ml) was added to the donor side. Levosimendan permeation from the gel-formulation was studied with Franz -diffusion chambers (DC-400, Crown Glass Co., Somerville, N.J.) at 25.degree. C. The volume of donor and receiver phases were 1 ml and 5 ml, respectively. Samples were withdrawn up to 72 h at fixed intervals and levosimendan concentration in samples was determined by HPLC (Beckman System Gold, Beckman Instruments Inc., CA). The HPLC column used was LiChrosorb RP-18 (7 .mu.m, 250 mm.times.4 mm), and the mobile phase was 55% of methanol and 45% of sodium phosphate buffer at **pH** 2,1. Detection wavelength was 360 nm and flow rate was 1.2 ml per min. Trans-dermal flux of levosimendan (.mu.g/h per cm.sup.2) across the skin was calculated using linear regression of the straight-line portion of drug permeation vs. time curve, and dividing by the surface area of the skin (0.64 cm.sup.2).

DETD TABLE 1
Permeation of levosimendan across human skin in vitro. Donor formulations buffered to **pH** 5 with sodium phosphate buffer. SLS = sodium lauryl sulphate, PG = propylene glycol, OA = oleic acid. % = % m/V.

Donor formulation	Conc. mg/ml	**pH**	Flux .+-. SD .mu.g/cm.sup.2 h	Lag time h
water + 90% ethanol	3.66	5.0	7.05 .+-. 1.11	15
water + 40% ethanol	1.73	5.0	0.87 .+-. 0.21	15
water + 10% ethanol + 0.01% SLS	0.061	5.0	0.43 .+-. 0.09	15
water + 10% ethanol + 0.01% SLS HPMC-gel (2.5%)	0.061	5.0	0.48 .+-. 0.15	15
water + 10% ethanol + 40% PG + 5% OA	1.19	5.0	16.0 .+-. 1.62	15
water + 0.1% SLS	0.061	5.0	5.25 .+-. 0.96	20
water + 1% SLS	0.49	5.0	25.38 .+-. 5.46	20

DETD Electrodes for iontophoresis were prepared from silver wire and silver chloride (Aldrich-Chemie, Steinheim, Germany). Direct current (0.5 mA/cm.sup.2) during iontophoresis was delivered by HP 6181C DC current source (Hewlett-Packard, CA) from the electrodes to the diffusion chambers via salt bridges. Salt bridges were prepared by injecting 1 M NaCl-gel (3% agar) inside plastic tubing (diameter 4 mm, length 15 cm).

Salt bridges prevented direct contact and possible reactions of levosimendan with Ag/AgCl-electrodes. HEPES-buffer at **pH** 7.4 was used in the receiver phase. Saturated levosimendan solution (3 ml) in HEPES-buffer (**pH** 7.4) was added to the donor side. AgCl-cathode was connected via the salt bridge to the donor solution. Positive silver anode was connected via the salt bridge to the receiver solution. The chambers were connected in series as constant DC-current was used. The Ag/AgCl-electrodes could be used continuously for 12 h. The results of this experiment are summarized in Table 2.

DETD TABLE 2

Penetration of levosimendan across human skin in vitro by iontophoresis (constant current 0.5 mA/cm.sup.2).

Donor solution	Conc. mg/ml	**pH**	Flux .+-. SD .mu.g/cm.sup.2 h	Lag time h
HEPES-buffer	0.41	7.4	2.87 .+-. 0.57	2

IT **141505-33-1**, Levosimendan
(transdermal compns. contg. levosimendan for treatment of heart failure)

L7 ANSWER 5 OF 8 USPATFULL

DETD The enantiomeric purities of the products were determined by the high performance liquid chromatography (HPLC,). The enantiomers of compound (II) were separated by using a cellulose-type chiral column (Chiralcel OJ 25.times.0.46 cm). The mobile phase consisted of ethanol. The flow rate was 0.5 ml/min. The enantiomers of compound (I) were separated by using a .beta.-cyclodextrin column (Cyclobond I Beta, 4.6.times.250 mm). The mobile phase consisted of 36% methanol in water buffered to **pH** 6.0 with 1% triethylammonium acetate. The flow rate was 0.8 ml/min.

DETD 100 g of racemic 6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone was added to 2997 ml of ethyl acetate, 94,4 ml of water, 77,8 g of D-tartaric acid and 1.0 g of D-tartaric salt of (-)-6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone under nitrogen. The mixture was stirred in room temperature for 1.5 h. Thereafter the mixture was heated to 65.degree. C. and stirred for 2 h. The precipitate was filtered hot and washed with 561 ml of ethyl acetate. The precipitate was mixed with 400 ml of water and **pH** of the mixture was adjusted to 9-10 with NH.sub.3. The mixture was cooled to 0.degree. C. and stirred for 2 h. The precipitate was filtered, washed three times with 322 ml of cold water and dried in vacuum in 50.degree. C. Yield was 35 g and the ratio of (-/+) enantiomers 93/7%. The product (35 g) was further added to 777 ml of acetonitrile and 2.0 g of celite under nitrogen. The precipitate was filtered hot and washed with 33 ml of acetonitrile which was added to the filtrate. 253 ml of acetonitrile was distilled from the filtrate and the remaining mixture was cooled to -5.degree. C. The precipitate was filtered, washed with 76 ml of acetonitrile and dried in vacuum in 50.degree. C. Yield 24.5 g. Ratio of (-/+) enantiomers 96/4%.

DETD 50 g of racemic 6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone was added to 1500 ml of ethyl acetate, 46 ml of water, 37.5 g of D-tartaric acid and 1.0 g of D-tartaric salt of (-)-6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone. The mixture was stirred in room temperature for 1.5 h. Thereafter the mixture was heated to 65.+-.3.degree. C. and stirred for 3 h. The precipitate was filtered hot and washed with 116 ml of ethyl acetate of room temperature. The precipitate was mixed with 200 ml of water of room temperature and 44 g of potassium bicarbonate in 90 ml of water was slowly added. It was checked that **pH** was over 9.0. The mixture was cooled to 0.+-.3.degree. C. and stirred for 2 h. The precipitate was filtered, washed three times with 120 ml of cold water and dried in vacuum in 50.+-.5.degree. C. Yield 17.87 g. Ratio of (-/+) enantiomers 90.7/8.6%.

DETD 50 g of racemic 6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2H)-

pyridazinone was added to 1500 ml of ethyl acetate, 45 ml of water and 37.3 g of L-tartaric acid. The mixture was heated to 60.degree. C. and stirred for 2 h. The precipitate was filtered and the filtrate was cooled to -10.degree. C. and kept in this temperature for 2 h. The precipitate that crystallized from the filtrate was filtered and dried in vacuum in 50.degree. C. The precipitate was mixed with 200 ml of water in room temperature and 43 g of potassium bicarbonate in 90 ml of water was slowly added. It was checked that **pH** was over 9.0. The mixture was cooled to 0.degree. C. and stirred for 2 h. The precipitate was filtered, washed three times with 120 ml of cold water and dried in vacuum in 50.+-.5.degree. C. Yield 20.61 g. Ratio of (-/+) enantiomers 78.7/21.2%.

IT 131741-08-7P **141505-33-1P**
(method for obtaining pure enantiomer of a pyridazinone deriv.)

L7 ANSWER 6 OF 8 USPATFULL
SUMM TABLE 1

The water solubility of (-) enantiomer and racemic mixture of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]propanedinitrile (I) in 67 mM phosphate buffer (**pH** 2).

Compound	Solubility (mg/ml)
(-) enantiomer	0.029
racemic	0.0007

DETD The optical purities of the compounds were determined by the high performance liquid chromatography. The instrument was a Waters 600 E gradient pump with a Waters 991 photodiode array detector and a Waters 700 Satellite Wisp injector (Millipore Co.) controlled by a NEC Powermate SX Plus computer. The enantiomers of 6-(4-aminophenyl)-5-methylpyridazin-3(2H)one were separated by using a sellulose-type chiral column (Chiracel=OJ, 4.6.times.250 mm, Daicel Chemical Industries LTD.). The mobile phase consisted of 97% 2-propanol and 3% hexane. The flow rate was 0.3 ml/min. The enantiomers of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile were separated by using a .beta.-cyclodextrin column (Cyclobond 1b, 4.6.times.250 mm, Advance Separation Technologies Inc.). The mobile phase consisted of 41% methanol in water buffered to **pH** 4.0 with 1% triethylammonium acetate. The flow rate was 0.3 ml/min.

IT **141505-33-1P** 144238-75-5P
(prepn. of, as cardiovascular agent)

L7 ANSWER 7 OF 8 USPATFULL
SUMM TABLE 1

The water solubility of (-) enantiomer and racemic mixture of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile (I) in 67 mM phosphate buffer (**pH** 2).

Compound	Solubility (mg/ml)
(-) enantiomer	0.029
racemic	0.0007

DETD The optical purities of the compounds were determined by the high performance liquid chromatography. The instrument was a Waters 600 E gradient pump with a Waters 991 photodiode array detector and a Waters 700 Satellite Wisp injector (Millipore Co.) controlled by a NEC Powermate SX Plus computer. The enantiomers of 6-(4-aminophenyl)-5-methylpyridazin-3(2H)one were separated by using a sellulose-type chiral

column (Chiracel=OJ, 4.6.times.250 mm, Daicel Chemical Industries LTD.). The mobile phase consisted of 97% 2-propanol and 3% hexane. The flow rate was 0.3 ml/min. The enantiomers of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile were separated by using a .beta.-cyclodextrin column (Cyclobond 1b, 4.6.times.250 mm, Advance Separation Technologies Inc.). The mobile phase consisted of 41% methanol in water buffered to **pH** 4.0 with 1% triethylammonium acetate. The flow rate was 0.3 ml/min.

IT **141505-33-1P** 144238-75-5P
(prepn. of, as cardiovascular agent)

L7 ANSWER 8 OF 8 USPATFULL
DETD TABLE 1

The water solubility of (-) enantiomer and racemic mixture of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]propanedinitrite (1) in 67 mM phosphate buffer (**pH** 2).

Compound	Solubility (mg/ml)
(-) enantiomer	0.029
racemic	0.0007

DETD The optical purities of the compounds were determined by the high performance liquid chromatography. The instrument was a Waters 600 E gradient pump with a Waters 991 photodiode array detector and a Waters 700 Satellite Wisp injector (Millipore Co.) controlled by a NEC Powermate SX Plus computer. The enantiomers of 6-(4-aminophenyl)-5-methylpyridazin-3(2H)one were separated by using a sellulose-type chiral column (Chiracel-OJ, 4.6.times.250 mm, Daicel Chemical Industries LTD.). The mobile phase consisted of 97% 2-propanol and 3% hexane. The flow rate was 0.3 ml/min. The enantiomers of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile were separated by using a .beta.-cyclodextrin column (Cyclobond 1b, 4.6.times.250 mm, Advance Separation Technologies Inc.). The mobile phase consisted of 41% methanol in water buffered to **pH** 4.0 with 1% triethylammonium acetate. The flow rate was 0.3 ml/min.

IT **141505-33-1P** 144238-75-5P
(prepn. of, as cardiovascular agent)

=> d l7 1-8

L7 ANSWER 1 OF 8 USPATFULL
AN 2002:129969 USPATFULL
TI Transmucosal formulations of levosimendan
IN Kurkela, Kauko, Espoo, FINLAND
Marvola, Martti, Helsinki, FINLAND
Larma, Ilkka, Springfield, NJ, United States
Virtanen, Raimo, Rusko, FINLAND
Karlsson, Marianne, Helsinki, FINLAND
PA Orion Corporation, Espoo, FINLAND (non-U.S. corporation)
PI US 6399610 B1 20020604
WO 9932081 19990701
AI US 2000-581610 20000831 (9)
WO 1998-FI977 19981211
20000831 PCT 371 date
PRAI FI 1997-4578 19971219
DT Utility
FS GRANTED
LN.CNT 281
INCL INCLM: 514/249.000
INCLS: 424/434.000; 424/435.000; 424/449.000; 424/451.000; 424/464.000

NCL NCLM: 514/249.000
NCLS: 424/434.000; 424/435.000; 424/449.000; 424/451.000; 424/464.000
IC [7]
ICM: A61K031-50
ICS: A61K009-14; A61F013-02
EXF 514/247; 424/449; 424/434; 424/451; 424/464; 424/435
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 2 OF 8 USPATFULL
AN 2002:50635 USPATFULL
TI Oral compositions of levosimendan
IN Backman, Maarit, Helsinki, FINLAND
Larma, Ilkka, Springfield, NJ, United States
Antila, Saila, Helsinki, FINLAND
Lehtonen, Lasse, Espoo, FINLAND
PA Orion Corporation, Espoo, FINLAND (non-U.S. corporation)
PI US 6355269 B1 20020312
WO 9916443 19990408
AI US 2000-509205 20000608 (9)
WO 1998-FI753 19980924
20000608 PCT 371 date
PRAI FI 1997-3804 19970926
DT Utility
FS GRANTED
LN.CNT 294
INCL INCLM: 424/464.000
INCLS: 514/247.000; 544/239.000
NCL NCLM: 424/464.000
NCLS: 514/247.000; 544/239.000
IC [7]
ICM: A61K009-20
ICS: A61K031-50; C07D237-02
EXF 424/464; 514/247; 544/239
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 3 OF 8 USPATFULL
AN 2002:14077 USPATFULL
TI Reference compound for use in the analysis of levosimendan batches
IN Backstrom, Reijo, Helsinki, FINLAND
Heinonen, Tuula, Espoo, FINLAND
Hauta-Aho, Tuula, Vantaa, FINLAND
PA Orion Corporation, Espoo, FINLAND (non-U.S. corporation)
PI US 6340764 B1 20020122
WO 9965888 19991223
AI US 2001-719806 20010220 (9)
WO 1999-FI539 19990618
20010220 PCT 371 date
PRAI FI 1998-1428 19980618
DT Utility
FS GRANTED
LN.CNT 266
INCL INCLM: 549/321.000
INCLS: 514/473.000; 552/001.000; 436/098.000; 436/093.000
NCL NCLM: 549/321.000
NCLS: 436/093.000; 436/098.000; 552/001.000
IC [7]
ICM: C07D307-32
ICS: G01N030-04; C07C247-00
EXF 549/321; 514/473
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 4 OF 8 USPATFULL
AN 2001:18019 USPATFULL
TI Transdermal compositions containing levosimendan

IN Urtti, Arto, Kuopio, Finland
Hirvonen, Jouni, Vantaa, Finland
Lehtonen, Lasse, Espoo, Finland
Antila, Saila, Helsinki, Finland
PA Orion Corporation, Espoo, Finland (non-U.S. corporation)
PI US 6183771 B1 20010206
WO 9801111 19980105
AI US 1999-214295 19990323 (9).
WO 1997-FI412 19970626
19990323 PCT 371 date
19990323 PCT 102(e) date
PRAI GB 1996-14098 19960705
DT Utility
FS Granted
LN.CNT 251
INCL INCLM: 424/449.000
INCLS: 424/448.000; 424/484.000; 424/486.000
NCL NCLM: 424/449.000
NCLS: 424/448.000; 424/484.000; 424/486.000
IC [7]
ICM: A61F013-02
ICS: A61K009-70; A61K009-14
EXF 424/402; 424/448; 424/449; 424/484; 424/486; 514/846
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 5 OF 8 USPATFULL
AN 2001:14644 USPATFULL
TI Method for obtaining pure enantiomers of a pyridazinone derivative
IN Timmerbacka, Mika, Veikkola, Finland
Lehtonen, Jorma, Kuohu, Finland
Tanninen, Veli Pekka, Espoo, Finland
Muttonen, Esa, Helsinki, Finland
Kaukonen, Jukka, Helsinki, Finland
Hyppola , Riikka, Espoo, Finland
Backstrom, Reijo, Helsinki, Finland
PA Orion Corporation, Espoo, Finland (non-U.S. corporation)
PI US 6180789 B1 20010130
WO 9735841 19971002
AI US 1999-155294 19990204 (9)
WO 1997-FI196 19970327
19990204 PCT 371 date
19990204 PCT 102(e) date
PRAI FI 1996-6474 19960327
DT Utility
FS Granted
LN.CNT 498
INCL INCLM: 544/239.000
INCLS: 514/247.000
NCL NCLM: 544/239.000
IC [7]
ICM: A61K031-50
ICS: C07D237-14
EXF 514/247; 544/239
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 6 OF 8 USPATFULL
AN 96:99209 USPATFULL
TI (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]propanedinitrile
IN Nore, Pentti, Helsinki, Finland
Honkanen, Erkki, Espoo, Finland
B ackstr om, Reijo, Helsinki, Finland
Wikberg, Tom, Espoo, Finland
Haikala, Heimo, Espoo, Finland

Haarala, Jorma, Helsinki, Finland
PA Orion-yhtyma Oy, Espoo, Finland (non-U.S. corporation)
PI US 5569657 19961029
AI US 1995-454856 19950531 (8)
RLI Division of Ser. No. US 1993-81360, filed on 30 Jun 1993, now patented, Pat. No. US 5424428, issued on 13 Jun 1995
PRAI GB 1991-49 19910103
GB 1991-189473 19910905
DT Utility
FS Granted
LN.CNT 262
INCL INCLM: 514/247.000
INCLS: 544/239.000
NCL NCLM: 514/247.000
NCLS: 544/239.000
IC [6]
ICM: A61K031-50
EXF 544/239; 514/247
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 7 OF 8 USPATFULL
AN 96:36567 USPATFULL
TI (-) [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]propanedinitrile
IN Nore, Pentti, Helsinki, Finland
Honkanen, Erkki, Espoo, Finland
Backstrom, Reijo, Helsinki, Finland
Wikberg, Tom, Espoo, Finland
Haikala, Heimo, Espoo, Finland
Haarala, Jorma, Helsinki, Finland
PA Orion-yhtyma Oy, Espoo, Finland (non-U.S. corporation)
PI US 5512571 19960430
AI US 1995-455035 19950531 (8)
RLI Division of Ser. No. US 1993-81360, filed on 30 Jun 1993, now patented, Pat. No. US 5424428, issued on 13 Jun 1995
PRAI GB 1991-49 19910103
GB 1991-18947 19910905
DT Utility
FS Granted
LN.CNT 253
INCL INCLM: 544/239.000
NCL NCLM: 544/239.000
IC [6]
ICM: C07D037-14
EXF 544/239
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 8 OF 8 USPATFULL
AN 95:52470 USPATFULL
TI (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]pr
IN Nore, Pentti, Helsinki, Finland
Honkanen, Erkki, Espoo, Finland
Backstrom, Reijo, Helsinki, Finland
Wikberg, Tom, Espoo, Finland
Haikala, Heimo, Espoo, Finland
Haarala, Jorma, Helsinki, Finland
PA Orion-yhtyma Oy, Espoo, Finland (non-U.S. corporation)
PI US 5424428 19950613
WO 9212135 19920723
AI US 1993-81360 19930630 (8)
WO 1992-FI3 19920103
19930630 PCT 371 date
19930630 PCT 102(e) date

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PRAI   GB 1991-49          19910103
       GB 1991-18947       19910905
DT     Utility
FS     Granted
LN.CNT 284
INCL   INCLM: 544/239.000
NCL    NCLM:  544/239.000
IC     [6]
       ICM: C07D037-14
EXF    544/239; 514/247
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


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     FILE 'REGISTRY' ENTERED AT 11:16:44 ON 27 MAY 2003
L1             1 S LEVOSIMENDAN/CN

     FILE 'REGISTRY' ENTERED AT 11:20:51 ON 27 MAY 2003
                 SET TERMSET E#
                 DEL SEL Y
                 SEL L1 1 RN
L2             1 S E1/RN
                 SET TERMSET LOGIN

     FILE 'MRCK' ENTERED AT 11:20:56 ON 27 MAY 2003
L3             1 S L2

     FILE 'CAPLUS' ENTERED AT 11:21:44 ON 27 MAY 2003
L4           113 S L1
L5             8 S L4 AND PH

     FILE 'USPATFULL' ENTERED AT 11:37:04 ON 27 MAY 2003
L6            10 S L1
L7             8 S L6 AND PH

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